REMARKS

I. Subject Matter of the Invention

The subject matter of the invention pertains generally to single chain proteins comprising a binding domain, an altered hinge peptide and immunoglobulin heavy chain CH2 and CH3 constant regions.

II. Objections to the Specification

The Examiner objects to the specification as containing hyperlinks. Applicants submit that these deficiencies were addressed in the substitute specification filed 10/28/03 and are no longer part of the specification.

The Examiner notes that Figures 7A-D were not described in the specification and that the status of USSN 07/723,454, and any other applications, should be updated. The specification has been amended accordingly, without introducing new matter.

III. Support for Amendments to the Claims

Support for the amendments to the claims can be found throughout the specification. For example, support for claim 23 can be found at page 24, line 15-18, which states that the number of cysteine residues in the hinge peptide is reduced by amino acid substitution or deletion, and at page 18, lines 13-17, which describes that the binding domain binds a target biological molecule. Support for the amendment to claim 24 is found, for example, at page 23, lines 21-26, which states that the hinge peptide may contain one cysteine.

Support for new claims 143 and 144 is found, for example, at page 29, line 26, to page 30, line 1, which teaches that an amino acid sequence contemplated by the invention may contain substitutions, including conservative substitutions. Support for new claim 145 is found, for example, in Example 5, page 74, lines 24-25, which teaches that the cysteine residues in the hinge peptide may be changed to serine residues.

The amendments to claims 44 and 47 were made to correct claim dependencies.

The amendments to the claims include no new matter.

IV. New Grounds of Objection/Rejection Not Based on Documents

The Examiner objects to the substitute specification filed October 28, 2003, asserting that the statement incorporating the priority document by reference is new matter. The first paragraph of the application has been amended to remove the incorporation by reference statement, thereby obviating the objection.

Claims 44 and 47 are objected to for depending on canceled claims. Claim 44 is additionally rejected for reciting the phrase "the protein," which the Examiner asserts is indefinite. Claims 44 and 47 have been amended accordingly.

Priority

The Examiner asserts that the priority document does not provide support for the present claims. Applicants submit that the priority application, U.S.S.N. 60/367,358, does provide support for the present claims.

The priority document describes a CD20 scFv fused to IgG1 hinge, CH2 and CH3 regions. Further, the priority document at page 11, lines 24-25 teaches that, in addition to 2H7scFv-Ig, other single chain Fv-Ig molecules are within the scope of the invention. The specification of the priority document describes methods of making scFv-Ig and techniques for making such molecules were known in the art at the time of filing the priority document. See Shan et al. *J. Immunol* 162:6589-95, 1999 (referenced at page 4, line 17-19 and relied upon by the Examiner).

The CD20 scFv Ig constructs and other single chain proteins described in the priority document support the present claims. Accordingly, Applicants request that the Examiner's assertion that the pending claims are not supported by the priority document be withdrawn.

V. Examiner's Grounds for Rejection Based on Publications

The Examiner variously rejected the claims under 35 U.S.C. §§102 or 103 as follows: claims 23-26 and 31-33 are rejected under 35 U.S.C. §102(e) as anticipated by Gillies et al., U.S. Patent. Publication 2003/0044423 (hereinafter "Gillies"); claims 39 and 142 are rejected under 35 U.S.C. §102(b) as anticipated by Shan et al., *J. Immunol* 162:6589-95, 1999 (hereinafter "Shan"); claims 23-28, 31-34, 39 and 142 are rejected under 35 U.S.C. §102(a) as anticipated by Wu et al., *Protein Engineering* 14:1025-33, 2001 (hereinafter "Wu");

claims 27-28, 34, 40-41, 44, 47 and 102-103 are rejected under 35 U.S.C. §103(a) as obvious over Gillies in view of Shan and Liu et al., *J. Immunol* 139:3521-26, 1987 (hereinafter "Liu"); claims 30, 35-36 and 38 are rejected under 35 U.S.C. §103(a) as obvious over Gillies in view of Kucherlapati et al., U.S. Patent 6,150,584 (hereinafter "Kucherlapati"), and Gilliland et al., *Tissue Antigens* 47:1-20, 1996 (hereinafter "Gilliland"); and claims 38 and 104-106 are rejected under 35 U.S.C. §103(a) as obvious over Gillies in view of Fell et al., *J Biol. Chem* 267:15552-58, 1992 (hereinafter "Fell"), and Gilliland.

VI. The Rejection of Claims 23-26 and 31-33 under 35 U.S.C. §102(e) as Anticipated by Gillies Should Be Withdrawn

The Examiner rejects claims 23-26 and 31-33 under 35 U.S.C. §102(e) as anticipated by Gillies. The Examiner argues that the Gillies application is entitled to a priority date of March 7, 2001, thereby antedating the actual filing date of the present application. As explained above, though, the present application is entitled to its priority date of January 17, 2001. Therefore, the present application has an earlier effective filing date than the Gillies provisional patent application. Thus, Gillies is not properly available as art against the pending claims.

Assuming *arguendo* that the present application is not entitled to its priority date, neither the Gillies priority document nor the Gillies published application describes the single chain proteins recited in the rejected claims.

Claims 23 and 24 are directed to single chain proteins having a binding domain, an altered hinge region containing either one or two cysteines (provided that when the altered hinge region contains two cysteines, the first cysteine found in the wild-type hinge is not deleted or substituted in the altered hinge), an Ig CH2 region polypeptide, and an Ig CH3 region polypeptide, where the single chain protein promotes ADCC and/or CDC function. The single chain proteins may comprise a binding domain that is an scFv (claim 26) or may bind to a target biological molecule on the surface of a cell (claim 25). Claims 31-33 are directed to single chain proteins wherein the single chain protein is capable of depleting a cell population or of decreasing the number of target cells in vivo or in vitro.

Gillies teaches antibody constructs having chimeric Fc regions which are designed to increase production and yield of the recombinant molecules. Gillies teaches that the hinge region of an Fc domain may be altered, stating that the hinge region preferably has two

cysteine residues rather than the three cysteine residues found in wild-type IgG1 hinges. According to Gillies paragraph 101, the cysteine in the hinge that is changed to another amino acid is the first cysteine in the hinge and the remaining two cysteines are not changed.

Gillies does not disclose any of the claim-recited hinge regions. The Gillies application describes altered hinge regions in which the first cysteine is changed to another amino acid and the second and third cysteines are retained, thus, the mutated hinge regions in Gillies differ from the claim-recited hinge regions. The rejected claims are directed to single chain proteins having an altered hinge region containing either one or two cysteines (provided that when the hinge region contains two cysteines the first cysteine is not deleted or substituted).

Moreover, the rationale behind the Gillies hinge mutations is different from that of the present invention. Gillies describes fusion proteins comprising Ig regions that are modified to increase recombinant protein yield, leading to assertedly improved purification processes. Particularly contemplated in Gillies are fusion proteins having "decreased" or "reduced" Fc effector functions. (Gillies provisional, page 5, 2nd full paragraph). This emphasis is explained in the Gillies application, which states in paragraph 115 that:

> "The utility of the invention is particularly illustrated in situations in which minimal binding to an Fc receptor I is desired. For example, in the context of fusion proteins, it is convenient to use the CH2 and CH3 regions from IgG2 because binding to FcR is profoundly reduced, so that ADCC is reduced and serum half-life is enhanced."

Thus, Gillies teaches that its of constructs benefit from having Fc regions that minimize or eliminate such effector functions as ADCC thereby extending serum half-life. Gillies even states that an absence of effector function is preferred. In contrast, the present invention is directed to single chain proteins which exhibit ADCC and/or CDC functions.

The rejection of claims 23-26 and 31-33 under 35 U.S.C. §102(e) over Gillies should therefore be withdrawn.

VII. The Rejection of claims 39 and 142 under 35 U.S.C. §102(b) as Anticipated by Shan Should Be Withdrawn

The Examiner rejects claims 39 and 142 under 35 U.S.C. §102(b) as anticipated by Shan. The Examiner appears to rely on Shan as disclosing a CD20-specific single chain antibody having V_H and V_L regions of the 1F5 antibody in single chain form linked to a

hinge, CH2 and CH3 region of IgG1. The hinge region of Shan contains no cysteine residues (p. 6590, col. 1).

Claims 39 and 142 are each ultimately dependent on claim 23 and/or claim 24, and claims 39 and 142 as amended are directed to a single chain protein having at least one cysteine residue in the hinge region. The Shan hinge region contains no cysteine residues. Therefore, Shan fails to disclose a recited feature of each of claims 39 and 142, and, as such, cannot anticipate the claimed subject matter. Accordingly, the rejection of claims 39 and 142 under 35 U.S.C. §102(b) over Shan should be withdrawn.

VIII. The Rejection of Claims 23-28, 31-34, 39 and 142 under 35 U.S.C. §102(a) as Anticipated by Wu Should Be Withdrawn

The Examiner rejects claims 23-28, 31-34, 39 and 142 under 35 U.S.C. §102(a) as anticipated by Wu. The Examiner appears to rely on Wu as disclosing a CD20-specific single chain antibody having a hinge, CH2 and CH3 region derived from IgG1, wherein the first hinge cysteine is mutated to serine (Wu page 1026, col, 2), but the second and third cysteines are retained.

Claim 23 is directed to a single chain polypeptide wherein that first hinge cysteine residue is specifically not substituted when the hinge contains two cysteine residues. Further, claim 24 is directed to a single chain protein having only one cysteine residue. Thus, Wu does not disclose each element of either claim 23 or 24. The remaining rejected claims ultimately depend from claims 23 and 24. Therefore, Wu does not anticipate any of claims 23-28, 31-34, 39 and 142, and the rejection of these claims under 35 U.S.C. §102(a) over Wu should be withdrawn.

IX. The Rejection of Claims 27-28, 34, 40-41, 44, 47, 102-103 under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner rejects claims 27-28, 34, 40-41, 44, 47, and 102-103 under 35 U.S.C. §103(a) as obvious over Gillies in view of Shan and Liu. The rejected claims are directed to single chain antibodies wherein the binding domain is specific for a B cell target biological molecule (claim 27), specifically CD20 (claim 28), and wherein the binding domain is derived from the 2H7 antibody (claims 40-41, 44, 47 and 102-103).

As noted by the Examiner, Gillies neither describes nor suggests a single chain polypeptide that binds to CD20. Further, as established in Section VI above, Gillies does not disclose a single chain protein as recited in claim 23 or 24 or in claims dependent thereon.

The Examiner characterizes Shan as describing a CD20-specific single chain antibody having a heavy chain hinge, and both CH2 and CH3 constant regions, wherein the hinge region contains no cysteine residues.

The Examiner interprets Liu as teaching the sequence of the 2H7 heavy and light chain variable regions. The chimeric antibody of Liu contains wild-type human IgG1 regions and Liu does not disclose or suggest making a single chain protein using these sequences. Liu also does not disclose or suggest mutating the IgG1 hinge region.

A person of ordinary skill in the art reading Gillies in view of Shan and Liu would not have been led to the single chain proteins recited in either claims 23 or 24 because none of the three references, considered alone or in any combination, discloses the hinge regions recited in either claim 23 or 24. Nor do the three cited references, alone or in combination, predict that such single chain proteins would retain ADCC and/or CDC function.

Claims 27-28, 34, 40-41, 44, 47 and 102-103, each ultimately depend on claim 23 and/or claim 24. Therefore, the subject matter of any of claims 27-28, 34, 40-41, 44, 47 and 102-103 is not obvious under 35 U.S.C. §103(a) over Gillies in view of Shan and Liu. Accordingly, the rejection should be withdrawn.

X. The Rejection of Claims 30, 35-36 and 38 under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner rejects claims 30, 35-36 and 38 under 35 U.S.C. §103(a) as obvious over Gillies in view of Kucherlapati and Gilliland.

The rejected claims are directed to a single chain protein specific for a B cell target (claim 30) or for various B cell targets and interleukins (claims 35-36), and to single chain proteins specific for various targets involved in cancer and other diseases or conditions (claim 38).

Gillies has been discussed above. Kucherlapati describes human single-chain antibodies derived from transgenic mice which may be specific for a variety of cell surface

markers, including B cell markers, interleukins and agents involved in cancerous conditions. Gilliland teaches methods for making scFv-Ig constructs for therapeutic applications.

As established in Section VI above, Gillies neither discloses nor suggests a single chain protein according to the present claims. Kucherlapati and Gilliland were cited as teaching that antibodies to many different antigens can be made in single-chain form, but (like Gillies) neither reference discloses or suggests making single chain proteins having hinge regions according to the present claims. A person of ordinary skill in the art reading Gillies in view of Kucherlapati and Gilliland would not have been led to the single chain proteins recited in either claim 23 or 24 because none of the three references, alone or in combination, discloses the hinge regions claimed. Nor do the three cited documents, considered alone or in combination, predict that such single chain proteins would retain ADCC and/or CDC function.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims and the rejection of claims 30, 35-36 and 38 under 35 U.S.C. §103(a) as obvious over Gillies in view of Kucherlapati and Gilliland should be withdrawn.

XI. The Rejection of Claims 48 and 104-106 under 35 U.S.C. §103(a) Should be Withdrawn

The Examiner rejects claims 48 and 104-106 under 35 U.S.C. §103(a) as obvious over Gillies in view of Fell and Gilliland. The rejected claims are directed to a single chain polypeptide specific for the L6 antigen.

Gillies and Gilliland have been discussed in Sections VI and X, respectively. Fell was relied upon as teaching generation of a chimeric L6-specific antibody. The chimeric antibody comprises the mouse L6 variable regions and human IgG1 heavy chain constant regions. Fell neither discloses nor suggests generation of a single chain antibody specific for the L6 antigen, nor does Fell suggest mutating the hinge region of the antibody. The combined disclosures of the three documents do not teach or suggest the single chain proteins of the present claims. A person of ordinary skill in the art reading Gillies in view of Fell and Gilliland would not have been led to the single chain proteins recited in claim 23 or 24 because none of the three documents, alone or in combination, discloses or suggests the hinge regions recited in the rejected claims. Nor do the three references, considered alone or in

combination, predict that such single chain proteins would retain ADCC and/or CDC function.

For the foregoing reasons, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims, and the rejection of claims 48 and 104-106 under 35 U.S.C. §103(a) as obvious over Gillies in view of Fell and Gilliland should be withdrawn.

XII. Conclusion

Applicants respectfully submit that the claims are in condition for allowance and request early notification of same.

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Respectfully submitted,

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